REMARKS AND ARGUMENTS

At the outset, Applicants acknowledge with appreciation the Examiner's withdrawal of the following rejections and objections made in the prior office action:

Claims 31-33, 43-41, and 43-45 under 35 USC §112, First Paragraph;

Claims 1-3, 5-9, 13-17, 19-23, 27-33, 35-39, and 43-45 under 35 USC §103 as being obvious over Bally and Curiel; and

Objections to the specification under 35 USC §132 regarding the Raines reference.

Objections to the Specification

The Examiner indicated that the specification was objected to under 35 USC §132 as allegedly incorporating new matter regarding the reference of Raines added in the previous amendment. Applicants herein delete the language referring to Ribonuclease I as shown in the above amended paragraphs, and now submit that this rejection is overcome.

Following entry of the present amendment, claims 1-3, 5-7, 13-17, 19-21, 27-33, 35-37, and 43-45 remain in the application for consideration. Claims 4, 12, 18, 26, 34, 42 and 46-57 were cancelled in the prior office action replies. Claims 8-12, 22-26, 38-42, and 58-78 are herein cancelled without prejudice.

Claims 1, 8, 15, 22, 30, 31, and 38 are herein amended. No new matter is added by these amendments.

Rejections under 35 USC §112

Claims 8, 11, 22, 25, 38, 41 64, 65, 74 and 75 were rejected under 35 USC §112, first paragraph, as allegedly containing new subject matter by the addition of "ribonuclease I". In view of the above cancelled claims, Applicants submit this rejection is now moot.

Claim 30 was rejected under 35 USC §112, second paragraph, as being indefinite. Applicants herein amend claim 30 to delete language including "pathophysiological conditions that depend on cells that can be detected or affected via target-mediated delivery of compunds" and now submit that this rejection is overcome.

Rejections under 35 USC §102

Claims 1-3, 5-7, 9, 13-17, 19-21, 23, 27-29, 31-33, 35-37, 39, and 43-45 were rejected under 35 USC §102(e) as being anticipated by US Patent No 6,284,742 to Curiel et al. Claims 1-3, 5-7, 9, 14-17, 19-21, 23 and 28 were also rejected under 35 USC §102(b) as being anticipated by WO 97/05266 to Valerio et al. Applicants respectfully traverse the rejections.

Curiel et al. disclose a delivery vehicle comprising an adenovirus encoding a gene of interest, a fiber-knob protein located on the adenovirus, and a bispecific antibody made from a first antibody which binds the fiber-knob protein and a second antibody that binds the CD40 antigen located on the surface of a cell.

Valerio et al. discloses a method and means for targeted gene delivery. In particular, the reference discloses a targeting gene delivery vehicle made from a virus, a binding pair such as an antibody/antigen or avidin/biotin, and a targeting conjugate that may be a fusion protein.

As now recited in amended claims 1, 15, and 31, the present invention is directed to a molecular delivery vehicle for delivery of compounds to a target, comprising, among other things, an adapter comprising a wild-type or mutant S-protein fragment of bovine or human ribonuclease A; and a recombinant targeting fusion protein comprising a recognition portion and a targeting portion, the recognition portion consisting essentially of a recognition peptide comprising an S-peptide fragment of bovine or human ribonuclease A, and capable of binding to said adapter, the targeting portion capable of binding to said target and comprising vascular endothelial growth factor 121.

Applicants submit that neither Curiel et al. nor Valerio et al. disclose or suggest an adapter comprising a wild-type or mutant S-protein fragment of bovine or human ribonuclease A or a recombinant targeting fusion protein comprising a recognition portion and a targeting portion, wherein the recognition portion consists essentially of a recognition peptide comprising an S-peptide fragment of bovine or human ribonuclease A, and the targeting portion comprising vascular endothelial growth factor 121 as specifically disclosed and claimed in the present invention. Accordingly, Applicants submit that Curiel et al. and/or Valerio et al do not anticipate the presently claimed invention, and that this rejection is overcome.

Rejections under 35 USC §103

Claim 30 was rejected as being unpatentable over Curiel et al. Applicants respectfully traverse the rejection.

Curiel et al. is discussed above. Claim 30 is herein amended to specifically recite, among other things, an adapter comprising a wild-type or mutant S-protein fragment of bovine or human ribonuclease A, and a recombinant targeting fusion protein comprising a recognition portion and a targeting portion, the recognition portion consisting essentially of a recognition peptide comprising an S-peptide fragment of bovine or human

ribonuclease A, and the targeting portion comprising vascular endothelial growth factor 121. Applicants submit that a combination of an S-peptide fragment of bovine or human ribonuclease A and VEGF factor 121 is neither disclosed or suggested by Curiel et al. Accordingly, Applicants submit that claim 30 is not obvious over Curiel et al., and that this rejection is overcome.

Claims 1, 8, 15, and 22 were rejected as being unpatentable over Valerio et al. in view of US Patent No. 5,506,121 to Skerra et al. Applicants respectfully traverse the rejection.

Valerio et al. is discussed above. Skerra et al. disclose methods and constructs for making fusion proteins and peptides with binding affinity for streptavidin.

Applicants submit that the combination of Valerio et al. and Skerra et al. does not disclose or suggested the invention as now claimed in amended claims 1 and 15. Specifically, Valerio et al do not disclose or suggest a molecular delivery vehicle, comprising, among other things, an adapter comprising a wild-type or mutant S-protein fragment of bovine or human ribonuclease A and/or a recombinant targeting fusion protein comprising a recognition portion and a targeting portion, wherein the recognition portion consists essentially of a

recognition peptide comprising an S-peptide fragment of bovine or human ribonuclease A, and wherein the targeting portion comprises vascular endothelial growth factor 121. Skerra et al. does not cure the deficiencies of Valerio et al. because Skerra et al. also does not disclose or suggest an adapter comprising a wild-type or mutant S-protein fragment of bovine or human ribonuclease A or a recognition portion consisting essentially of a recognition peptide comprising an S-peptide fragment of bovine or human ribonuclease A, and a targeting portion comprising vascular endothelial growth factor 121. Accordingly, Applicants submit that the presently claimed invention is not obvious over the combination of Valerio et al. and Skerra et al., and therefore this rejection is overcome.

Claims 1, 10, 13, 15, 24, 27, 58-63, 66-73, and 76-77 were rejected as being obvious over Valerio et al. (discussed above) in view of US Patent Application publication No. US 2001/038851 to Allen et al. and US Patent No. 5,194,596 to Tischer et al. Applicants respectfully traverse the rejection.

Allen discloses a therapeutic liposome composition that includes pre-formed liposomes having an entrapped therapeutic agent and a plurality of targeting conjugates composed of a lipid, a hydrophilic polymer, and a targeting ligand. Table 1

shows a variety of possible targeting ligand-receptor pairs including VEGF.

Tischer et al. discloses methods and means for obtaining commercial scale quantities of vascular endothelial cell growth factor for use as a wound healing agent. Tischer et al. further disclose several VEGF types, including bovine VEGF having 120 amino acids and human VEGF having 121 amino acids.

At the outset, Applicants submit that claims 58-63, 66-73, and 76-77 are herein cancelled and therefore this rejection is moot with respect to these claims. With respect to claims 1, 10 13, 15, 24, and 27, Applicants submit that this combination of references does not make the present invention obvious.

As presently claimed, the invention is directed to a molecular delivery vehicle for delivery of compounds to a target, comprising, among other things, an adapter comprising a wild-type or mutant S-protein fragment of bovine or human ribonuclease A and a recombinant targeting fusion protein having a recognition portion and a targeting portion, the recognition portion consisting essentially of a recognition peptide comprising an S-peptide fragment of bovine or human ribonuclease A, and the the targeting portion comprising vascular endothelial growth factor 121.

Applicants submit that none of the cited references, taken either individually or in combination, disclose or suggest an adapter comprising a wild-type or mutant S-protein fragment of bovine or human ribonuclease A and/or a recombinant targeting fusion protein made from S-peptide fragment of bovine or human ribonuclease A, and vascular endothelial growth factor 121. Applicants submit that a recombinant targeting fusion protein having the combination of S-peptide fragment of bovine or human RNase A and VEGF 121 is neither disclosed nor suggested from any of the cited references. Accordingly, Applicants submit that claims 1, 10, 13, 15, 24, and 27 are not obvious over the cited references, and that this rejection is overcome.

Claims 1, 8, 11, 15, 22, and 25 were rejected as being obvious over Valerio et al. in view of US Patent No. 6.075,010 to Theodore et al. Applicants respectfully traverse the rejection.

Valerio et al. is discussed above. Theodore et al. disclose small molecular weight clearing agents containing ligands such as biotin or biotin analogs and hexose residues. The disclosed clearing agents clear anti-ligand containing conjugates in vivo through hepatocyte receptor mediated clearance mechanisms. Theodore et al. further disclose use of

S-peptide/S-protein complementary binding pair members in pretargeting methods.

Applicants submit that none of the references, taken individually or in combination, disclose or suggest the presently claimed invention. As indicated above, none of the references disclose or suggest an adapter comprising a wild-type or mutant S-protein fragment of bovine or human ribonuclease A in combination with a recombinant targeting fusion protein made from S-peptide fragment of bovine or human ribonuclease A, and vascular endothelial growth factor 121. Applicants submit that a recombinant targeting fusion protein having an adapter comprising a wild-type or mutant S-protein fragment of bovine or human ribonuclease A and the combination of S-peptide fragment of bovine or human RNase A and VEGF 121 is neither disclosed nor suggested from any of the cited references, and therefore these references do not make the presently claimed invention recited in claims 1, 8, 11, 15, 22 and 25 obvious. Accordingly, Applicants submit that this rejection is overcome.

Claims 58, 64, 65, 68, 74, and 75 were rejected as being unpatentable over Valerio et al., Allen et al., and Tischer et al., as applied to claims 1, 10, 13, 15, 24, 27, 58-63, 66-73, and 76-77, and further in view of Theodore et al.

Applicants submit that claims 58, 64, 65, 68, 74, and 75 are herein cancelled, and therefore this rejection is moot. However, Applicants respectfully submit that as applied to claims 1, 10, 13, 15, 24, and 27, the combination of Valerio et al., Allen et al., Tischer et al., and Theodore et al. does not make the present invention obvious.

Applicants submit that none of the cited references, taken individually or in combination teach or suggest a molecular delivery vehicle comprising, among other things, an adapter comprising a wild-type or mutant S-protein fragment of bovine or human ribonuclease A in combination with a recombinant targeting fusion protein comprising a recognition portion and a targeting portion, wherein the recognition portion consists essentially of a recognition peptide comprising an S-peptide fragment of bovine or human ribonuclease A, and the targeting portion comprising vascular endothelial growth factor 121.

In contrast, Valerio et al. disclose chemical modification of proteins with avidin or biotin to form the so-called targeting conjugate (see page 13, lines 13-36 and page 14, lines 5-35). These chemically modified structures are distinguishable from the recombinant targeting fusion protein that is disclosed and specifically claimed in the present invention. Similarly, while Valerio et al. discloses fusion proteins in the context of

leucine zipper terminal domains (page 16, lines 8-15), there is no disclosure directed to the a recombinant product made from an S-peptide fragment of bovine or human ribonuclease A, and vascular endothelial growth factor 121. Moreover, none of the other cited references (Allen et al., Tischer et al., and Theodore et al.) disclose or suggest a recombinant product made from an S-peptide fragment of bovine or human ribonuclease A, and vascular endothelial growth factor 121. Accordingly, Applicants submit that the presently claimed invention is not obvious in view of any combination of Valerio et al., Allen et al., Tischer et al., and Theodore et al., and that this rejection is overcome.

Claims 29-37, 39, 44, and 45 were rejected as being unpatentable over Valerio et al. in view of Curiel et al. For the reasons outlined above, Applicants submit that this rejection is overcome.

Claims 38 and 41 were rejected as being unpatentable over Valerio et al and Curiel et al., as applied to claims 29-37, 39, 44, and 45, and further in view of Theodore et al. For the reasons outlined above, Applicants submit that this rejection is overcome.

Claims 40 and 43 were rejected as being unpatentable over Valerio et al., and Curiel et al., as applied to claims 29-37,

39, 44 and 45, and further in view of Allen et al., and Tischer et al. For the reasons outlined above, Applicants submit that this rejection is overcome.

Claims 1-3, 5-9, 13-17, 19-23, 27-33, 35-39, and 43-45 were rejected as being unpatentable over US Patent No. 4,885,172 to bally et al., in view of Valerio et al and Skerra et al. Applicants respectfully traverse the rejection.

Valerio et al. and Skerra et al. are discussed above. Bally et al. disclose a composition for targeting, storing and loading of liposomes consisting of liposomes covalently or non-covalently coupled to the glycoprotein streptavidin. The streptavidin is coupled to biotinylated proteins made by chemical modifications. Examples of such chemically modified proteins include biotinylated immunoglobulin G or biotinylated monoclonal antibodies.

Applicants submit that the presently claimed invention is not obvious in view of Bally et al., Valerio et al, and/or Skerra et al.

As indicated above, none of the references disclose or suggest an adapter comprising a wild-type or mutant S-protein fragment of bovine or human ribonuclease A and a recombinant targeting fusion protein made from S-peptide fragment of bovine or human ribonuclease A, and vascular endothelial growth factor

121. Applicants submit that a moiety having an adapter comprising a wild-type or mutant S-protein fragment of bovine or human ribonuclease A and a recombinant targeting fusion protein having the combination of S-peptide fragment of bovine or human RNase A and VEGF 121 is neither disclosed nor suggested from any of the cited references, and therefore these references do not make the presently claimed invention obvious. Accordingly, Applicants submit that this rejection is overcome.

Claims 10, 24, 40, 58-64, 66-74, and 76-78 were rejected as being unpatentable over Bally et al. and Skerra et al. as applied to claims 1-3, 5-9, 13-17, 19-23, 27-33, 35-39, and 43-45 above, and further in view of Allen et al. and Tischer et al.

For the reasons outlined above, Applicants submit that this rejection is overcome.

Claims 11, 25, 41, 65, and 75 were rejected as being obvious over Bally et al., Valerio et al., and Skerra et al. as applied to claims 1-3, 5-9, 13-17, 19-23, 27-33, 35-39, and 43-45 and further in view of Theodore et al.

As indicated above, none of the references disclose or suggest a recombinant targeting fusion protein made from S-peptide fragment of bovine or human ribonuclease A, and vascular endothelial growth factor 121. Applicants submit that an adapter comprising a wild-type or mutant S-protein fragment of

bovine or human ribonuclease A and a recombinant targeting fusion protein having the combination of S-peptide fragment of bovine or human RNase A and VEGF 121 is neither disclosed nor suggested from any of the cited references, and therefore these references do not make the presently claimed invention obvious. Accordingly, Applicants submit that this rejection is overcome.

In view of the above amendments and remarks, Applicants submit that the claims are in condition for allowance, and respectfully request reconsideration and early receipt of a Notice of Allowance.

If a telephone conference would aid in the continued prosecution of this application, the Examiner is invited and encouraged to contact Applicants' representative at the telephone number listed below.

Respectfully submitted,

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